Solvent-Dependent Mixed Complex Formation—NMR Studies and Asymmetric Addition Reactions of Lithioacetonitrile to Benzaldehyde Mediated by Chiral Lithium Amides

Richard Sott, Johan Granander, and Göran Hilmersson*[a]

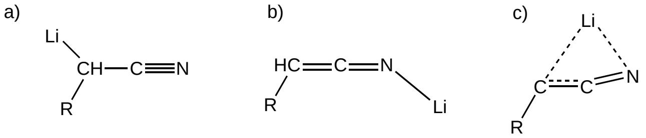
Abstract: Lithioacetonitrile and a chiral lithium amide with an internally coordinating methoxy group form mixed dimers in diethyl ether (DEE) and in tetrahydrofuran (THF) according to NMR studies. Based on the observed ^{6}Li,^{1}H heteronuclear Overhauser effects, in THF lithioacetonitrile is present in a mixed complex with the chiral lithium amide, and this complex has a central N-Li-N-Li core. In DEE, on the other hand, the acetonitrile anion bridges two lithiums of the dimer to form a central six-membered Li-N-C-C-Li-N ring. Gauge individual atomic orbital DFT calculations of the ^{13}C NMR chemical shifts of the DEE- and THF-solvated mixed dimers show good agreement with those obtained experimentally. Lithioacetonitrile complexed to the chiral lithium amide has been employed in asymmetric addition to benzaldehyde in both DEE and THF. In THF the product, (*S*)-3-phenyl-3-hydroxy propionitrile, is formed in 55% *ee* and in DEE the *R* enantiomer is formed in 45% *ee*. This change in stereoselectivity between solutions in DEE and THF was found to be general among a number of different chiral lithium amides, all with an internal chelating methoxy group.

Keywords: asymmetric synthesis · density functional calculations · enantioselectivity · lithium complexes · solvent effects

Introduction

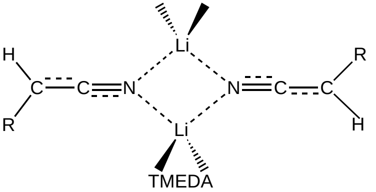
The chemistry of cyano-stabilized carbanions has been widely employed in organic synthesis; this is underscored by the large number of publications devoted to the field.[1–3] The addition of cyano-stabilized carbanions to aldehydes gives access to the versatile synthetic intermediates β-hydroxy nitriles. These can be transformed into γ-amino alcohols, which are useful synthetic building blocks and common in prescribed antidepressants.[4–6]

The monomeric structures of these carbanions have been widely discussed, and *C*-metalated carbanions, *N*-metalated ketenimines, and bridged types, shown in Scheme 1, have all been suggested.[7, 8] However, these organometallic species generally aggregate in solution, and a small number of reports on lithiophenylacetonitrile have shown dimeric complexes in both tetrahydrofuran (THF) and dimethyl sulfoxide.[8–11]



Scheme 1. Suggested structures of lithiated nitriles: a) *C*-metalated carbanion, b) *N*-metalated ketenimine, and c) bridged type.

The structure of these α-nitrile-stabilized organolithium species did not become known in detail until Boche et al. reported the first X-ray study of solvated lithiophenylacetonitrile.[12] It was shown that lithiophenylacetonitrile was present as an *N*-metalated ketenimine in a homo-dimer solvated by *N,N,N′,N′*-tetramethylethylene diamine (TMEDA), as in Scheme 2. Detailed solution studies of lithiophenylacetonitrile by NMR spectroscopy by Collum et al. with ^{6}Li,^{15}N scalar couplings showed an *N*-lithiated ketenimine dimer to be present in diethyl ether (DEE)/toluene and a TMEDA-solvated dimer to be present in toluene.[13] No ^{6}Li,^{15}N couplings were resolved for solutions in tetrahydrofuran. They also observed that a mixed dimer was formed between doubly labeled [^{6}Li,^{15}N]-lithium hexamethyldisil-



Scheme 2. X-ray structure of lithiophenylacetonitrile found by Boche et al.[12]

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azide and [^{6}Li,^{15}N]-phenylacetonitrile solvated by TMEDA; this was similar to the complex found by Boche et al.

In contrast to the extensive use of lithiated nitriles in organic synthesis, there are to our knowledge only a few examples of diastereoselective and even fever examples of enantioselective applications.[14] The first enantioselective application with lithioacetonitrile was reported by Soai and Mukaiyama.[15] Later they achieved higher selectivity with cyanomethylzinc bromide.[16] Recently, Carlier reported the deprotonation of arylacetonitriles and their subsequent diastereoselective addition to aldehydes, although he named this class of reactions aldol reactions.[14, 17, 18]

Here we wish to report on the solution structures of the aggregates formed from lithioacetonitrile and the chiral lithium amide Li-[2-methoxy-(*R*)-1-phenyl][(*S*)-1-phenylethyl]amide (Li−**1**) in THF and DEE.[19, 20] We have also studied (*S*)-*N*-isopropyl-*O*-ethylphenyl glycinol (Li−**2**) and compared the structure and reactivity of these two ligands. The structures were determined based on NMR spectroscopy accompanied by computational (semi-empirical and DFT) methods. The results of stereoselective addition of lithioacetonitrile to benzaldehyde by using several different chiral lithium amides as chiral inducers are also reported.

Results

NMR Studies of Li−1: Addition of *n*Bu[^{6}Li] to acetonitrile in THF or DEE at −78 °C resulted in several signals in the ^{13}C and ^{6}Li NMR spectra at −90 °C. These signals are probably from mixed dimers and tetramers of *n*BuLi and lithioacetonitrile. Further addition of *n*Bu[^{6}Li] at −78 °C completed the rapid formation of lithioacetonitrile, which has low solubility in both DEE and THF. The presence of Li−**1** prevented precipitation of lithioacetonitrile; this indicates either reaction with Li−**1** or the formation of a mixed complex. Addition of acetonitrile to Li−**1** results in the formation of lithioacetonitrile, since acetonitrile is more acidic than **1**.

THF: One equivalent of acetonitrile was added to an NMR tube loaded with a 1:1 mixture of Li−**1** and *n*Bu[^{6}Li] in [D$_8$]THF at −78 °C. Two ^{6}Li NMR signals at $\delta = 0.84$ and $\delta = 0.97$ of equal intensity, independent of concentration (0.02 to 0.20 M), were observed at −90 °C. To establish that these two lithium signals arose from a single complex, we performed a ^{6}Li,^{6}Li EXSY experiment at −90 °C. From the cross-peak-to-diagonal-peak intensities, the rate constant for the lithium exchange was determined to be $0.47 \pm 0.03\ \text{s}^{-1}$, corresponding to a $\Delta G^{\neq}$ (176 K) of $10.4 \pm 0.1\ \text{kcal mol}^{-1}$.[21] The coalescence temperature of the two peaks was found to be −72 °C at both 0.02 and 0.2 M. The ^{13}C NMR spectra of the mixed aggregate were different from those of **1** and (Li−**1**)$_2$.[20] One set of signals from lithioacetonitrile was observed at different shifts from those of pure lithioacetonitirile. The signal at $\delta = -1.9$ was assigned to the α carbon of lithioacetonitrile complexed to Li−**1**, and the broad signal at $\delta = 157.3$ was assigned to the carbon of the cyano group. The measured ^{13}C,^{1}H coupling constant of the α carbon of lithioacetonitrile in the mixed dimer complex was 163 Hz. The magnitude of the coupling constant suggests that the carbanion is mainly sp^2 hybridized in THF. No ^{13}C,^{6}Li couplings were observed between −60 and −110 °C (experiments performed in THF/DEE 1:1). Further addition of Li−**1** resulted in monomeric Li−**1** at $\delta = 1.6$ in the ^{6}Li NMR spectra.[20] The ^{13}C NMR chemical shifts of **1** and its aggregate forms are given in Table 1.

The ^{6}Li,^{1}H HOESY experiments showed no NOE's between the CH$_2$ protons of lithioacetonitrile at $\delta = 0.4$ and the two lithiums, see Figure 1. However, heteronuclear Over-

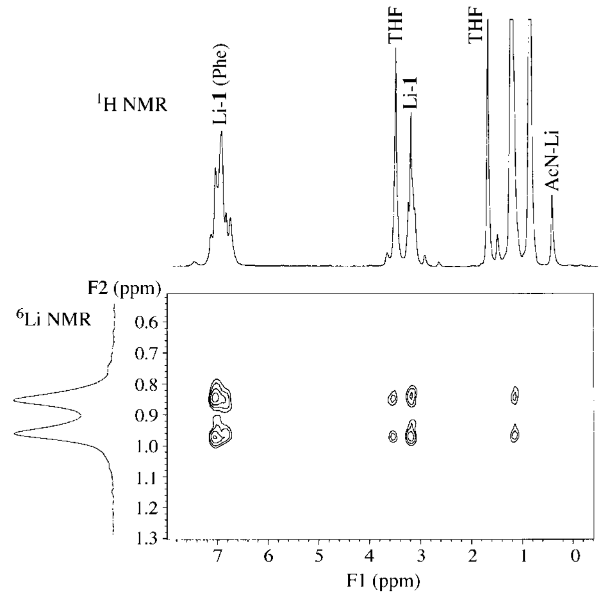


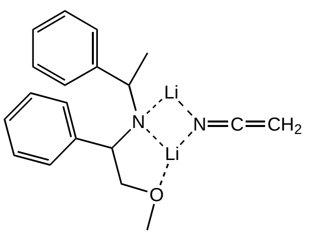
Figure 1. The ^{6}Li,^{1}H HOESY spectrum of a 1:1 mixture of lithioacetonitrile and Li−**1** obtained at −90 °C in THF.

Table 1. Selected ^{13}C NMR chemical shifts for **1** and its aggregate forms at −80 °C.

Structure	δ^b (CN, AcNLi)	δ^b(C	C	CH$_2$	CH	CH	OCH$_3$)	δ^b(CH$_2$, AcNLi/*n*BuLi)
THF								
1		146.9	142.3	78.8	59.7	58.6	55.3	
Li−**1**/BuLi		154.0	148.3	81.5	66.9	61.6	58.8	12.6 (quintet)
(Li−**1**)$_2$		155.2	149.4	80.8	68.9	63.1	59.6	
Li−**1**/AcN-Li	157.3	153.6	147.4	81.5	66.4	62.2	58.8	−1.9
DEE								
1		146.2	141.5	78.6	59.4	58.6	54.9	
Li−**1**/BuLi		152.2	147.8	82.0	66.4	60.7	59.2	11.8 (quintet)
(Li−**1**)$_2$		154.6	148.2	79.4	64.7	62.3	58.7	
Li−**1**/AcN-Li[a]	149.5	151.4	146.9	82.2	66.2	59.1	58.7	−7.2

[a] The ^{13}C NMR spectrum was recorded at −85 °C.

hauser effects between the two lithium signals and the aromatic proton signals of complexed Li–**1** were observed. Altogether this suggests a mixed dimer complex of lithioacetonitrile and Li–**1** with a Li-N-Li-N central core in THF, shown in Scheme 3. Apparently there should be no observed NOE's between the α-protons of lithioacetonitrile and the lithiums due to the large distances.



Scheme 3. Proposed solvent structure of the mixed aggregate of the lithiated acetonitrile and Li–**1** dimer in THF.

DEE: The NMR spectra of mixtures of Li–**1** and lithioacetonitrile in DEE were not as simple as those in THF. However, two major ^{6}Li NMR signals at $\delta = 1.1$ and $\delta = 2.8$ in a 1:1 ratio were observed at −90 °C. The signal intensities were concentration independent (0.02 to 0.20 M). A set of small unassigned signals (<10 %) was also observed at $\delta =$ 0.4, 1.6, and 3.1. However, strong cross peaks between the signals at $\delta = 1.1$ and $\delta = 2.8$ were observed in ^{6}Li,^{6}Li EXSY experiments performed at −50, −60, and −65 °C; these were also independent of concentration (0.02 to 0.20 M). From the cross-peak-to-diagonal-peak intensities at −60 °C, the rate constant for the intra-aggregate exchange was determined to be $0.3 \pm 0.05\,s^{-1}$, corresponding to a $\Delta G^{\neq}$ (176 K) = 12.8 ± 0.1 kcal mol^{-1}.[21] In the ^{13}C NMR spectra obtained at −90 °C one major set of signals was observed at different shifts from those of (Li–**1**)$_2$ and Li–**1**/*n*BuLi.[20] There were only traces of signals from the amine **1** in the ^{13}C and ^{1}H spectra. Addition of more than one equivalent of **1** and *n*BuLi[^{6}Li] resulted in the formation of (Li–**1**)$_2$ and Li–**1**/*n*BuLi. Only one set of signals was observed from lithioacetonitrile. The broad signal at $\delta = -7.2$ was assigned to the α carbon and the other broad signal at $\delta = 149.5$ was assigned to the cyano-group carbon of lithioacetonitrile. The large solvent dependence in chemical shift for the α carbon of lithioacetonitrile ($\delta = -7.2$ in DEE and −1.9 in THF at −90 °C) is consistent with a structure that has higher electron density at the α carbon than the one proposed to exist in THF solution. The ^{13}C NMR chemical shifts of **1** are again given in Table 1. The α carbon signal was broad in DEE but no ^{13}C,^{6}Li coupling was resolved at any temperature between −60 and −110 °C; this is probably due to fast dynamics in solution. The ^{13}C,^{1}H coupling constant of the β carbon signal, 150 Hz measured at −90 °C, was smaller than expected for a sp^2 carbon (typically values are 160–170 Hz) and smaller than that of the corresponding dimer in THF, but significantly larger than that of acetonitrile.

The ^{6}Li,^{1}H HOESY experiments revealed heteronuclear Overhauser effects between both lithium signals ($\delta = 1.1$ and $\delta = 2.8$) and the CH$_2$ protons of lithioacetonitrile at $\delta = 0.6$, as well as the proton signals from Li–**1**, shown in Figure 2. This suggests a nonsymmetrical arrangement of lithioacetonitrile in the dimer in which the acetonitrile anion bridges between two lithiums. The unresolved ^{13}C,^{6}Li couplings may be explained by a dynamic exchange between the two bridged structures displayed in Scheme 4.

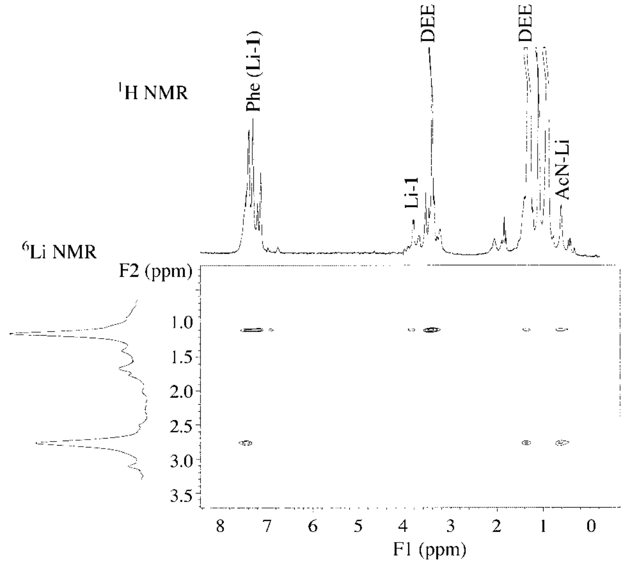
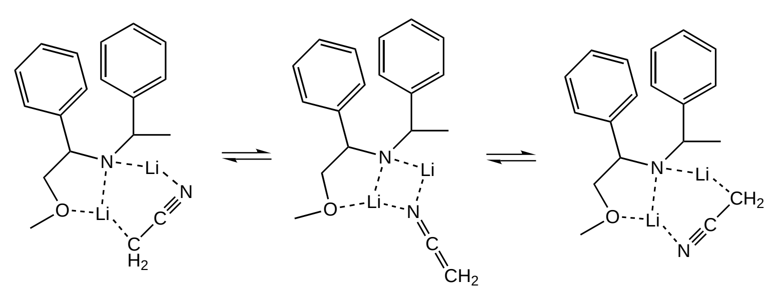


Figure 2. HOESY spectrum of the mixed aggregate formed by lithioacetonitrile and Li–**1** in DEE at −80 °C, showing NOE's between the ^{6}Li signals at $\delta = 1.1$ and $\delta = 2.8$ and the proton signals from Li–**1** and lithioacetonitrile.

[^{15}N]-labeled acetonitrile was employed in the attempts to unambiguously determine the position of metalation of lithioacetonitrile in the mixed complex with Li–**1** in order to observe ^{6}Li,^{15}N coupling. A 0.2 M solution of [^{6}Li]-**1** and [^{15}N,^{6}Li]-acetonitrile was prepared. No ^{6}Li,^{15}N couplings were observed for any of the lithium signals of the mixed complexes in either THF or DEE solution. The absence of scalar ^{15}N,^{6}Li couplings at temperatures between −50 and −110 °C indicates fast chemical exchange within the complexes.[22, 23] However, the ^{6}Li resonances of the DEE solvate were broad and could possibly contain unresolved splittings. In previous



Scheme 4. Suggested structure and dynamics of the mixed aggregate of lithioacetonitrile and Li–**1** in DEE.

studies, Li–**1** has been shown to be predominantly dimeric in DEE and monomeric in THF. However, we can not rule out the possibility of larger aggregates, especially in DEE.

NMR Studies of Li–2: The chiral lithium amide Li–**2** in a mixed complex with lithioacetonitrile was examined by ^{1}H, ^{13}C, and ^{6}Li NMR spectroscopy in both DEE and THF. The studies in DEE were similar to those of Li–**1**/lithioacetonitrile with two signals at $\delta = 2.7$ and 1.1 of equal intensities in the ^{6}Li NMR spectrum at $-70\,^\circ$C. Signals at $\delta = 149.3$ and $\delta = -7.4$ in the ^{13}C NMR spectrum and at $\delta = 0.6$ in the ^{1}H NMR spectrum indicated complexed lithioacetonitrile. Correlations in the ^{6}Li,^{1}H HOESY experiment at $-70\,^\circ$C showed NOE's between the lithioacetonitrile protons and both lithium signals in DEE, similar to the ^{6}Li,^{1}H HOESY spectra of Li–**1** in DEE. The THF-solvated mixture of Li–**2** and lithioacetonitrile resulted in two ^{6}Li NMR signals at $\delta = 0.9$ and $\delta = 0.7$ of equal intensity, ^{13}C NMR signals at $\delta = 157.1$ and $\delta = -2.1$, and a ^{1}H NMR signal at $\delta = 0.3$ at $-80\,^\circ$C. To our surprise, the ^{6}Li,^{1}H HOESY experiment at $-70\,^\circ$C in THF was also similar to that of Li–**1** in DEE, with correlations between the lithioacetonitrile protons and both lithium signals. The studies of Li–**2** and lithioacetonitrile in DEE and THF both indicate the formation of a mixed-dimer complex, similar to that of Li–**1** and lithioacetonitrile in DEE.

Computational Studies of Li–1/lithioacetonitrile: A computational approach was employed to gain further insight into the structure of the mixed dimer between Li–**1** and lithioacetonitrile solvated by ethers. Due to the considerable size of the aggregates including the solvation, we restricted our full geometry optimizations to semi-empirical PM3 calculations with dimethyl ether replacing DEE and THF.[24] Two different mixed dimers with a bridging acetonitrile anion are possible, one with the chelating methoxy group on the lithium bonded to the nitrile nitrogen and another with the methoxy group on the lithium bonded to the CH_2 carbon. In this study, only dimers with tetracoordinated lithium atoms were considered. The model systems named **A1**, **A2**, and **A2′** are displayed in Figure 3. We also performed full DFT geometry optimizations on the smaller model systems **B1**, **B2**, and **B2′** at the B3LYP/6–31G(d) level of theory.[25] DFT single-point calculations at the MPW1PW91/6–31+G(d) level of theory were performed on both the PM3- and the B3LYP/6–31G(d)-optimized structures.[26]

From the results of the calculations we concluded that the six-membered ring dimer with a bridging CH_2CN unit appears to be the most stable complex among **A1**, **A2**, and **A2′**. The **A2** structure is surprisingly 5.9 kcal mol^{-1} lower in energy than **A2′**. However, at the DFT level of theory for the simpler **B** systems we found that the **B2** arrangement is slightly higher in energy (1.0 kcal mol^{-1}) than **B2′**. In contrast to the calculations of **A1**, **A2**, and **A2′**, we found that the ketenimine mixed dimer **B1**, with the planar lithioacetonitile, is more stable than **B2′** by 1.3 kcal mol^{-1}. However, the energy differences are small and do not allow the exclusion of any of these structures. Clearly this chemical computational study of a model system does not represent all the experimental conditions. Calculations that include solvent continuum effects have been found to be important.[27]

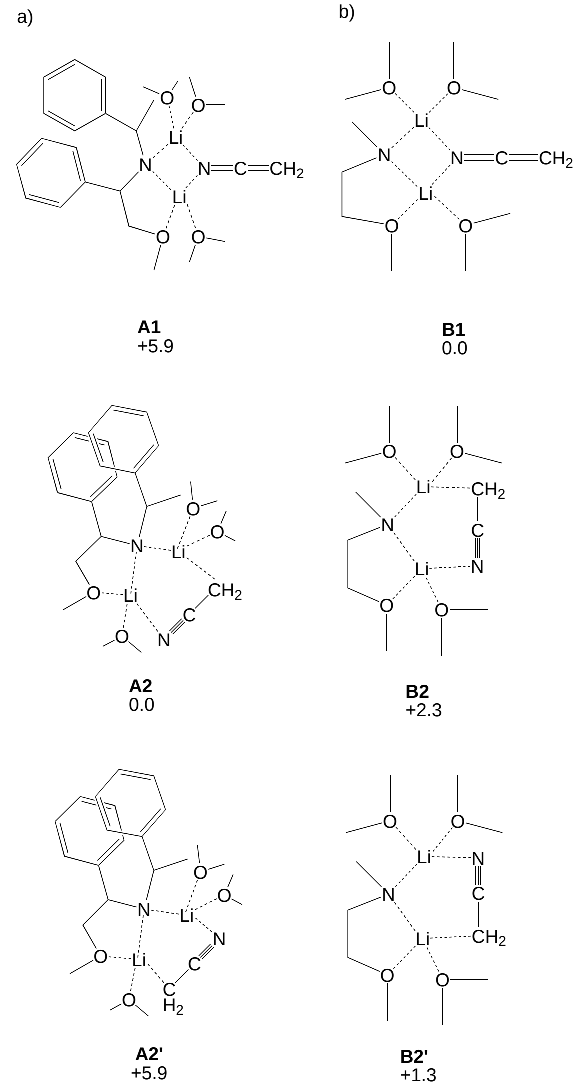


Figure 3. a) Geometry-optimized structures **A1**, **A2**, and **A2′** at the PM3 level of theory followed by a single-point calculation at the MPW1PW91/6–31+G(d) level, given as relative energies (kcal mol^{-1}). b) Geometry-optimized structures **B1**, **B2**, and **B2′** at the B3LYP/6–31G(d) level of theory followed by a single-point calculation at MPW1PW91/6–31+G(d), given as relative energies (kcal mol^{-1}).

Selected Li–H distances of the calculated structures **A1** and **A2** are given in Table 2. These distances are approximate,

Table 2. Selected Li–H distances [Å] measured in the calculated structures **A1** and **A2**.

	A1		**A2**	
proton	methoxy coord. lithium	ether coord. lithium	methoxy coord. lithium	ether coord. lithium
CH_2=C=N	4.81	4.88	4.54	2.69
-CH_2-O-CH_3	3.27	4.96	2.89	4.97
-CH-CH_3	3.71	2.65	4.02	2.51
-CH-CH_3	2.50	3.15	2.67	2.77
-CH-CH_2O-	3.89	3.99	3.81	3.76
-OCH_3	2.98	4.31	3.04	4.62
Aromatics	3.19	3.03	2.97	2.44

but they indicate the relative proximities that support the observed Li–H NOE's. Strong NOE's are expected for Li–H distances of 2–3 Å. From the calculations on **A1**, it is evident that no NOE's are expected between the protons of lithioacetonitrile and the lithiums due to the long distance (4.8 Å).

The isotropic shielding values were calculated by using the gauge individual atomic orbital (GIAO) method at the MPW1PW91/6–31+G(d)//PM3 and MPW1PW91/6–31+G(d)//B3LYP/6–31G(d) levels of theory.[26, 28–30] The corresponding chemical shifts were referenced to tetramethylsilane. TMS was optimized at the B3LYP/6–31G(d) level of theory and its GIAO isotropic shift was calculated at MPW1PW91/6–31+G(d). The calculated shifts of acetonitrile in the PM3-optimized mixed dimers **A1**, and **A2** are shown in Table 3 along with those of the DFT-optimized mixed dimers **B1**, **B2**, and **B2′**. The calculated shifts of the α carbon of ketenimine structures **A1** and **B1** were similar with values of $\delta = -0.2$ and $\delta = -0.9$ (cf. $\delta_{exp} = -1.9$). The calculated shifts of the α carbon of the bridged acetonitrile in **A2**, **B2**, and **B2′** appear more upfield with values of $\delta = -7.0$, -10.4, and -8.5 (cf. $\delta_{exp} = -7.2$).

Table 3. Observed and calculated ^{13}C NMR chemical shift[a] of the CH_2 carbon of lithioacetonitrile in mixed dimers.

Structure	δ^b (CH_2-carbon)	δ^b (CN-carbon)
Observed		
in DEE	−7.2	149.5
in THF	−1.9	157.3
Calculated		
A1[b]	0.2	162.3
A2[b]	−7.0	141.3
A2′[b]	−2.6	140.4
B1[c]	−0.9	154.9
B2[c]	−10.4	140.6
B2′[c]	−8.5	141.7

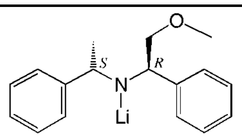
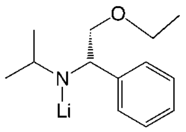
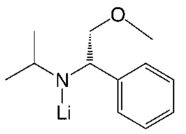
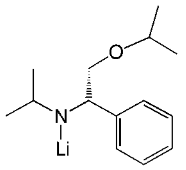
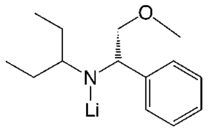
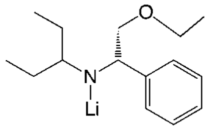
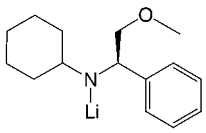
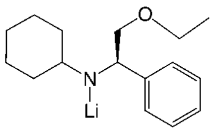
[a] Relative to TMS ($\delta = 0.0$). [b] Geometry optimized at the PM3 level of theory followed by a single-point calculation at the MPW1PW91/6–31+G(d) level. [c] Geometry optimized at the B3LYP/6–31G(d) level of theory followed by a single-point calculation at MPW1PW91/6–31+G(d).

Furthermore, the good agreement between the calculated chemical shift of the carbon of the nitrile (δ_{calc} **A1** = 162.3 and δ_{calc} **B1** = 154.9) and that observed in THF solution (δ_{exp} = 157.3) suggests that the *N*-lithiated ketenimine dimer dominates in THF. These values are also significantly different from those calculated for the mixed dimers with a bridging CH_2CN unit (δ_{calc} **A2** = 141.3, δ_{calc} **A2′** = 140.4, δ_{calc} **B2** = 140.6, and δ_{calc} **B2′** = 141.7). These calculated chemical shifts for the mixed dimers with a bridging CH_2CN unit are close to the experimental value of 149.5 observed in DEE.

Asymmetric addition of lithioacetonitrile to benzaldehyde: The lithiation of acetonitrile with *n*BuLi proceeds quickly at −116 °C in either THF or DEE. Benzaldehyde was added to the 2:1 mixtures of the chiral lithium amides and lithioacetonitrile at −116 °C. The reaction mixture was quenched with methanol after 30 minutes and analyzed by using capillary gas chromatography on chiral stationary phase. The results of the asymmetric nucleophile addition of acetonitrile to benzaldehyde at −116 °C by using different chiral lithium amide bases are summarized in Table 4. Note that not all amides have the same relative configuration at the stereogenic center next to the nitrogen. Two different solvent systems were employed: DEE and a 1:1 mixture of DEE and THF. The reason for using a DEE/THF solvent mixture was simply to prevent the THF from freezing. Only minor effects from the DEE are expected, since THF is known to coordinate much more strongly to lithium than DEE does.

In DEE, the enantiomeric excesses range from 4 to 45% when these different chiral lithium amides are used as chiral inducers. The largest enantiomeric excesses were observed for the amides containing the bulkier substituents on the nitrogen, cyclohexyl, or 1-phenylethyl. However, there is no simple correlation between the size of the hydrocarbon substituent on the amide nitrogen and the *ee* of the product. All amides yield low to moderate selectivity, that is, 4 to 45% *ee* of 3-hydroxy-3-phenylpropionitrile of the same configuration as

Table 4. Resulting *ee*'s from the asymmetric addition of acetonitrile to benzaldehyde at −116 °C by using different chiral lithium amides.

	amide	config.	*ee*	
			in DEE	in DEE/THF
1		(*R*)	45.0 (*R*)	54.8 (*S*)
2		(*S*)	30.3 (*S*)	13.0 (*S*)
3		(*S*)	4.1 (*S*)	55.0 (*R*)
4		(*S*)	34.0 (*S*)	22.6 (*S*)
5		(*S*)	27.8 (*S*)	17.1 (*R*)
6		(*S*)	22.2 (*S*)	14.1 (*S*)
7		(*R*)	30.5 (*R*)	48.8 (*S*)
8		(*R*)	42.8 (*R*)	10.0 (*R*)

the chiral lithium amide used. The highest selectivity, 45% *ee*, was achieved by using Li–**1**, see entry 1 in Table 4.

Employing THF/DEE resulted in large variations in selectivity. The enantiomer of the product with the same stereo configuration as the lithium amide used was only formed when using the amides with the slightly larger alkyl group on the oxygen (ethyl or isopropyl). The stereoselectivity was rather poor ranging from 10 to 23% *ee* (entries 2, 4, 6, and 8).

However, to our surprise, all the methoxy ether amides generated the opposite relative stereo configuration of the product, see entries 1, 3, 5 and 7. The stereochemical addition reaction is thus reversed with these amides, yielding selectivities between 17 and 55% *ee*. Thus these amides exhibit a unique solvent dependence since the stereochemical outcome of the addition reaction was inverted from DEE solution to the DEE:THF mixture. The use of (*R*)-Li–**1** produced (*S*)-3-hydroxy-3-phenylpropionitrile with 55% *ee* in the DEE:THF mixture, but in DEE a 45% *ee* of the *R* enantiomer was observed. Thus Li–**1** represents a unique catalyst that is able to invert the stereochemistry of the addition product depending on the solvent used.

Discussion

The quantum chemical calculations of ^{13}C NMR chemical shifts showed differences between the two proposed dimeric complexes formed between lithioacetonitrile and Li–**1** in THF and in DEE. In THF, the ^{6}Li,^{1}H HOESY experiments suggested that the mixed complex was an *N*-lithiated ketenimine dimer. In DEE on the other hand, the α carbon of lithioacetonitrile must be in close proximity to the lithiums, since strong heteronuclear Overhauser effects were observed. This strongly suggests that DEE promotes the formation of a 6-membered ring structure with a bridging acetonitrile anion. The DFT GIAO-computed α-carbon chemical shifts of the model systems **B2** and **B2′**, $\delta = -10$ and $\delta = -8.5$, were close to the experimentally observed value of $\delta = -7.2$. Fast intra-aggregate exchange between the possible mixed dimers of the chiral lithium amide and lithioacetonitrile may explain the broad unresolved ^{13}C and ^{6}Li NMR signals. Although the DFT calculations suggests that the planar ketenimine structure should be favored in the mixed dimer with the chiral lithium amide, all other results strongly argue for the bridging acetonitrile arrangement. One should also remember that the calculated in vacuo energy difference between the calculated structures is small. However, the DFT-GIAO results are very promising as a tool for the elucidation of structures and aggregates of organolithium complexes. The two bridging structures **B2** and **B2′** give similar values (-10 and -8.5) for the ^{13}C NMR chemical shifts of the two carbons of lithioacetonitrile in the mixed complex. The DFT-computed chemical shifts of both the α carbon and the nitrile carbon of lithioacetonitrile in the proposed mixed dimers are in good agreement with those experimentally observed in THF and DEE.

In contrast to the NMR studies of Li–**1**/lithioacetonitrile, we found that Li–**2** formed 6-membered ring structures with a bridging acetonitrile anion in both DEE and THF. The stereoconfiguration of the alkylation product of the reaction mediated by Li–**2** is solvent independent; this was general among the *O*-ethylated and *O*-isopropylated amides. The *O*-methylated amides, on the other hand, produced alcohols with the same stereoconfiguration in DEE and opposite stereoconfiguration in THF. This indicates that the lithium amides that form 6-membered ring structures with lithioacetonitrile produce alcohols with the same stereoconfiguration, while *N*-lithiated ketenimine structures result in the opposite stereoconfiguration.

Asymmetric additions of lithioacetonitrile to benzaldehyde mediated by a chiral lithium amide yielded selectivities up to 55%. This does not represent a synthetically useful selectivity but the addition showed a very strong solvent dependence with 45% *ee* of the *R* product in DEE but 55% *ee* of the *S* product in DEE/THF with (*R*)-Li–**1**.

Conclusion

Lithioacetonitrile forms mixed dimeric complexes with Li–**1** in THF and DEE. NMR experiments suggest an *N*-lithiated ketenimine dimer in THF, which is different from the six-membered ring complex formed in DEE. These chiral complexes are potentially useful for enantioselective addition to aldehydes, especially since the stereoselectivity can be inverted by changing solvent. Although it has been shown previously that lithiophenylacetonitrile exists as an *N*-lithiated dimer both in solution and in the solid state, our results have shown that mixed complexes between a chiral lithium amide and a lithiated nitrile anion may also consist of a bridging acetonitrile anion. Such a bridging acetonitrile anion coordination has to our knowledge only been reported in a dimeric lanthanide complex.[31]

Experimental Section

General: Glassware and syringes were dried at 50°C in a vacuum oven before transfer into a glove box (Mecaplex GB80 equipped with a gas purification system that removes oxygen and moisture) under a nitrogen atmosphere. Typical moisture content was less than 1.5 ppm. All manipulations concerning the addition reactions were carried out by using gas-tight syringes. Ethereal solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in septum-sealed flasks inside the glove box. Acetonitrile was distilled from CaH_2 and further dried over molecular sieves.

[2-methoxy-(*R*)-1-phenylethyl][2-[^{6}Li]-lithium-(*S*)-1-phenylethyl] amide (Li–1) in situ preparation: The preparation and characterization of this lithium amide has been reported previously.[19, 20]

NMR Instrumental: All NMR spectra were recorded on a Varian Unity500 spectrometer equipped with three channels and a 5 mm ^{1}H, ^{13}C, ^{6}Li triple resonance probe head built by the Nalorac Company. Measuring frequencies were 500 MHz (^{1}H), 125 MHz (^{13}C), and 73 MHz (^{6}Li). The ^{1}H and ^{13}C spectra were referenced to the solvent signals: [D$_{10}$]diethyl ether at $\delta = 1.06$ (^{1}H -CH$_3$) and δ 65.5 (^{13}C -CH$_2$), and [D$_8$]THF at δ 1.72 (^{1}H -CH$_2$) and $\delta = 25.4$ (^{13}C -CH$_2$). Probe temperatures were measured after more than 1 hour of temperature equilibrium with both a calibrated methanol–freon NMR thermometer and the standard methanol thermometer supplied by Varian instruments.[32] ^{6}Li,^{1}H HOESY experiments were performed with $\tau_M = 1.0$ s in both THF and DEE. ^{6}Li,^{6}Li EXSY spectra were recorded with $\tau_M = 0.5$ s in THF and $\tau_M = 1.5$ s in DEE. For further data of the ^{6}Li,^{1}H HOESY experiments, see previous studies of Li–**1**.[20]

Computational methods: Due to the considerable size of the aggregates under investigation, we restricted our geometry optimizations to semi-empirical PM3 calculations.[21, 22] However, geometry optimizations were also performed on smaller model systems at the B3LYP/6–31G level of theory. All geometries were characterized as minima by calculation of their frequencies. All the GIAO DFT ^{13}C NMR chemical-shift calculations were performed at the MPW1PW91/6–31+G(d) level of theory.[26, 28–30] The calculations were performed either by using the Titan[33] program package or the Windows-based Gaussian98[34] program package on a Pentium 4 1400 MHz PC.

Asymmetric addition reactions: A septum-sealed flask containing a magnet, the amine (0.20 mmol), and dry DEE or THF/DEE (1:1) (2.0 mL) was assembled inside the glove box. The flask was taken out and directly fitted with a dry argon inlet. The flask was cooled to $-116\,^{\circ}$C (DEE/N$_2$(l)) for 10 min before *n*BuLi (0.30 mmol in hexane) was added dropwise with a syringe. After an additional 10 min, acetonitrile (0.10 mmol in dry toluene) was added dropwise to the solution. The lithiation of acetonitrile was complete in 1 h at $-116\,^{\circ}$C. Benzaldehyde (0.05 mmol in dry toluene) was slowly added with a syringe. The reaction was quenched after 30 min by the addition of methanol (1.0 mL). The crude mixture was neutralized with 10 % HCl, extracted with DEE, and analyzed by using chiral stationary-phase GC. The chromatograms showed that the reactions were close to quantitative with respect to the amines and that the addition products together with traces of 1-phenylpentan-1-ol were the only detected compounds. The assignment of the two resolved peaks in the chiral GC chromatogram was made by comparison with that of enantiomerically pure (*S*)-3-hydroxy-3-phenylpropionitrile synthesized from (*R*)-styrene epoxide.[5]

Chromatographic analyses were carried out by using a Varian Star 3400 CX gas chromatograph. All GC analyses were run on a chiral stationary-phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. Analyses were done with He (1.5 mL min^{-1}) as carrier gas (injector 225 °C, detector 250 °C). The column temperature was 150 °C. The retention times were 18.5 min for (*R*)-3-hydroxy-3-phenylpropionitrile and 20.2 min for (*S*)-3-hydroxy-3-phenylpropionitrile.

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